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d-LIVER

ICT-enabled, cellular artificial liver system incorporating personalized patient management and support

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D1.5: Specification of essential clinical parameters predicting individual outcome

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1. Executive summary

End stage liver disease (ESLD) is associated with poor outcome [1]. Liver transplantation is considered to be a viable therapy for patients with end-stage liver disease but due to an increasing incidence of liver disease and the chronic shortage of donor organs, the length of time patients spend waiting for a liver transplant is increasing [2]. Not all patients will benefit from liver transplantation [3, 4] and there is therefore a need for scoring systems which can help to accurately estimate an individual's need for transplantation and the expected long term outcome. The scores commonly used at present have significant limitations; the Child-Pugh score includes subjective parameters (grade of ascites and encephalopathy) while the MELD score includes serum creatinine, which reflects renal function rather than being a direct measure of liver function [5, 6]. There is therefore a requirement for more objective scoring systems to estimate patient mortality and severe morbidity. In addition, new methods need to be explored to support or replace liver function at the point of need.

Within d-LIVER Task 1.3, variables which could be useful to indicate enrolment of patients to the d-LIVER system were evaluated based on the accuracy of prediction of short-term survival. A prospective cross-sectional observational study was started at the Charité University Hospitals enrolling patients with end-stage liver disease to collect the conventional clinical and laboratory parameters as well as data on actual liver function as measured by maximal enzymatic liver function capacity (LiMAx test).

This deliverable proposes a novel scoring system including an estimation of actual liver function for the stratification of patients according to disease severity for the estimation of short-term mortality. This novel survival model, comprised of enzymatic liver function and serum creatinine levels for the assessment of short-term prognosis, shows comparable prognostic value to the Model for End Stage Liver Disease (MELD) and might be useful in clinical practice for selected patients.

2. Introduction

Deliverable D1.3 reported preliminary data of this prospective cross-sectional cohort study. The final analysis of the data is presented in this deliverable report.

As in D1.3, the Background section serves to allow the reader to become familiar with the complex situation of end-stage liver failure patient, the objective graduation of disease severity and organ allocation.

Section 3 will give the reader a short introduction and overview of the disease pattern of chronic liver failure and therapeutic options. In addition, currently used scoring systems are described highlighting their strengths and weaknesses.

Section 5 outlines the study concept and protocol of the clinical trial undertaken at Charité University Hospital.

Section 6 reports the final results, the prediction of individual outcome and the suggestion of a novel survival model, considering enzymatic liver function and serum creatinine levels.

Section 7 discusses current findings and their implications for the d-LIVER management system.

3. Background and current concepts in liver allocation

Since the first successful liver transplantation in 1967, more than 170,000 liver transplantations have been performed worldwide [7]. Liver transplantation has become the therapy of choice for most forms of end-stage liver disease (ESLD) [8]. Survival rates after liver transplantation have increased dramatically since the first procedures due to improvements in immunosuppressive drugs, surgical techniques, organ preservation and peri-operative care [9, 10]. Most of these improvements occurred during the first 35 years of liver transplantation with few additional improvements over the last decade. A “chronic” shortage of donor organs is partly responsible for the increased use of so-called marginal organs (organs of decreased quality e.g. organs from old donors, donors with infectious diseases) and the waiting time for organ transplantation is getting longer with MELD scores of patients on transplant lists increasing as a result [11, 12]. Thus there is a greater demand for new methods to support or replace liver function at the point of need. Moreover, the currently used scoring system for organ distribution – the MELD Score – has limitations. Alternative approaches have been suggested that either refine the MELD by incorporating additional prognostic parameters [13], adjust the formula [14], or indeed replace MELD with an alternative system [15]. Although the implementation of MELD in 2002 led to a significant reduction in waiting list mortality [16], certain cohorts of patients may be disadvantaged by MELD-based liver allocation [17]. In addition to deranged liver function tests, high serum creatinine [18] and hyponatremia [19] represent good predictors of outcome in cirrhotic patients. However, it can be argued that single serum parameters are relatively easy to manipulate (e.g. international normalized ratio (INR) will increase with the use of anticoagulants, serum sodium may be influenced by diuretic therapy while creatinine levels are unreliable in patients undergoing dialysis) and might only represent surrogate markers for the actual functional state of the liver. Thus an appropriate question to be raised is whether the consideration of enzymatic liver function as an objective and robust parameter provides additional information on the short-term prognosis of patients with ESLD.

Initial work has shown that LiMAx, a novel ^{13}C-based test for the determination of maximum liver function capacity, is useful for the assessment of individual risk prior hepatic surgery [20, 21]. Recently its predictive value has been reported in patients with acute liver failure [22] and patients with bacterial sepsis [23]. Thus it seems reasonable to evaluate LiMAx in patients with

chronic liver disease and to investigate the diagnostic accuracy of estimation of short-term prognosis in patients with ESLD in a prospective cross-sectional cohort study.

3.1. Prediction of outcome

Cirrhosis of the liver is associated with high rates of morbidity and mortality [1]. Scoring systems have been developed which estimate the risk of mortality allowing stratification of patients for liver transplantation. However, these scores are based on standard biochemical tests and clinical signs of liver insufficiency. In particular, scoring systems such as Child Turcotte Pugh Score (CPS) or MELD score reflect symptoms and complications of ESLD, rather than being a direct representation of liver function [5, 6]. Thus little is known about the association between actual liver function and the prognosis of patients with liver cirrhosis.

3.1.1. Scoring systems in clinical practice

Child Turcotte Pugh Score / CP classes

This scoring system was originally developed to predict survival among cirrhotic patients after portosystemtic shunt operations for portal hypertension [6, 24]. Until 2002 entrance criteria for admission to the waiting list for liver transplantation were based on this score.

Based on 5 parameters (3 laboratory parameters and 2 clinical parameters) the Child Turcotte Pugh Score (CPS) categorizes patients into 3 classes according to the sum of the individual findings. Rates of morbidity and mortality (one year survival) differ between groups (Group A – low risk; Group B – intermediate risk; Group C – high risk).

Calculation: Each measure is scored 1-3 according to the severity of impairment, indicating 3 as the most severe derangement (Table 1).

Table 1: Child-Turcotte Pugh scoring system.

Measure	1 point	2 points	3 points
Total bilirubin (µmol/l)	< 34	34 - 50	> 50
Serum albumin (g/l)	> 35	28 - 35	< 28
INR	< 1.7	1.71 – 2.30	> 2.30
Ascites	None	Mild	Severe
Hepatic Encephalopathy	None	Grade I – II	Grade III - IV

Interpretation: Patients with chronic liver disease are classified as Class A, B or C.

5-6 points → Class A patients have a 3-year survival of 73%

7-9 points → Class B patients have a 3-year survival of 59%

10-15 points → Class C patients have a 3-year survival of 46% [25]

The major limitation of the CPS is that it includes the grading of ascites and encephalopathy, which are relatively subjective findings.

MELD

The allocation of deceased donor livers for transplantation in Europe and the United States is now based on the severity of illness as determined by MELD [6, 26]. The score is derived from a linear regression model based on:

- serum bilirubin
- serum creatinine
- international normalized ratio (INR)

It is calculated according to the following formula:

$$\{MELD = 3.78(\ln Bil) + 11.2(\ln INR) + 9.57(\ln Cr) + 6.43\}$$

(Bil = Bilirubin (mg/dL), INR= International Normalised Ratio, Cr = Creatinine (mg/dL))

Figure 1: Formula for calculation of MELD

The United Network for Organ Sharing (UNOS) has made modifications to the score. For example, if the patient has been dialyzed twice within the last 7 days, the value for serum creatinine used, should be 4.0mg/dL [27].

In interpreting the MELD Score in hospitalized patients, the 3-month mortality is approximately:

- 40 or more → 71.3% mortality
- 30–39 →52.6% mortality
- 20–29 → 19.6% mortality
- 10–19 → 6.0% mortality
- <9 →1.9% mortality [26]

MELD Na and United Kingdom model for End-Stage Liver Disease (UKELD)

MELD-Na was created using nationwide waiting list registration data from the United Network for Organ Sharing [13, 29]. In 2005 and 2006, the Mayo Clinic developed and validated a multivariable survival model to predict mortality at 90 days after registration. The predictor variable was the Model for End-Stage Liver Disease (MELD) score with the addition of the serum sodium concentration. In addition to the MELD score, the serum sodium concentration has been recognized as an important prognostic factor in patients with liver cirrhosis [30]. For example, hyponatremia has been associated with the hepatorenal syndrome, ascites and death from liver disease.

In the UK transplant centres use the so-called UKELD score to evaluate the risk of mortality without transplantation. The score is derived from patient INR, serum creatinine, serum bilirubin and serum sodium (Figure 2). With a UKELD score of 49 patients have approximately a 9% one year mortality while a UKELD score of 60 is predictive of a 50% one-year mortality [30].

$$\{UKELD = 5.395(\ln INR) + 1.485(\ln Cr) + 3.13(\ln Bil) - 81.565(\ln Na) + 435\}$$

(Bil = Bilirubin (µmol/L), INR = International Normalised Ratio, Cr = Creatinine (µmol/L), Na = Sodium (mmol/L)).

Figure 2: Formula for calculation of UKELD

4. Aims of study

The aims of this prospective cross-sectional observational study were to evaluate the prognostic value of liver tests and established scores regarding transplant-free survival and mortality. Beyond that this study aimed to determine new scoring systems which include measures of liver function.

5. Patients and Methods

This section is confidential and so is not included in this version of the document.

6. Results

This section is confidential and so is not included in this version of the document.

7. Discussion

This section is confidential and so is not included in this version of the document.

8. Conclusions

In conclusion, in addition to the currently used MELD, this work suggests a novel scoring system be incorporated into the d-LIVER management system for the individual (and liver function oriented) stratification of patients at increased risk of short-term mortality. Moreover, it is suggested that, by consideration of the current MELD and the reported novel predictive method, patients with previous episodes of clinical decompensation (HE/ascites) should also be included in the d-LIVER treatment concept.

References

1 Everhart JE Digestive Diseases in the United States: epidemiology and impact. NIH Publication 1994:94-1447.

2 Olthoff KM, Brown RS, Jr., Delmonico FL, Freeman RB, McDiarmid SV, Merion RM, *et al.* Summary report of a national conference: Evolving concepts in liver allocation in the MELD and PELD era. December 8, 2003, Washington, DC, USA. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2004;**10**:A6-22.

3 Lake JR Evaluation and management of prospective liver transplant candidates. In: Norman DJ, Turka LA, eds. Primer on Transplantation. 2nd ed. Mt. Laurel, N.J.: American Society of Transplantation, 2001: 523-8.

4 Merion RM. When is a patient too well and when is a patient too sick for a liver transplant? Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2004;**10**:S69-73.

5 Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, *et al.* Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;**124**:91-6.

6 Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;**31**:864-71.

7 Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the Liver in Humans. Surgery, gynecology & obstetrics 1963;**117**:659-76.

8 Starzl TE, Iwatsuki S, Van Thiel DH, Gartner JC, Zitelli BJ, Malatack JJ, *et al.* Evolution of liver transplantation. Hepatology 1982;**2**:614-36.

9 Neuberger J. Developments in liver transplantation. Gut 2004;**53**:759-68.

10 Adam R, Cailliez V, Majno P, Karam V, McMaster P, Caine RY, *et al.* Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. Lancet 2000;**356**:621-7.

11 Tector AJ, Mangus RS, Chestovich P, Vianna R, Fridell JA, Milgrom ML, *et al.* Use of extended criteria livers decreases wait time for liver transplantation without adversely impacting posttransplant survival. Annals of surgery 2006;**244**:439-50.

12 Foster R, Zimmerman M, Trotter JF. Expanding donor options: marginal, living, and split donors. Clinics in liver disease 2007;**11**:417-29.

13 Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, *et al.* Hyponatremia and mortality among patients on the liver-transplant waiting list. The New England journal of medicine 2008;**359**:1018-26.

14 Sharma P, Schaubel DE, Sima CS, Merion RM, Lok AS. Re-weighting the model for end-stage liver disease score components. Gastroenterology 2008;**135**:1575-81.

15 Schaubel DE, Guidinger MK, Biggins SW, Kalbfleisch JD, Pomfret EA, Sharma P, *et al.* Survival benefit-based deceased-donor liver allocation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2009;**9**:970-81.

16 Brown RS, Jr., Lake JR. The survival impact of liver transplantation in the MELD era, and the future for organ allocation and distribution. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2005;**5**:203-4.

17 Biggins SW, Bambha K. MELD-based liver allocation: who is underserved? Seminars in liver disease 2006;**26**:211-20.

18 Fernandez-Esparrach G, Sanchez-Fueyo A, Gines P, Uriz J, Quinto L, Ventura PJ, *et al.* A prognostic model for predicting survival in cirrhosis with ascites. Journal of hepatology 2001;**34**:46-52.

19 Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005;**41**:32-9.
20 Stockmann M, Lock JF, Riecke B, Heyne K, Martus P, Fricke M, *et al.* Prediction of postoperative outcome after hepatectomy with a new bedside test for maximal liver function capacity. Annals of surgery 2009;**250**:119-25.
21 Stockmann M, Lock JF, Malinowski M, Niehues SM, Seehofer D, Neuhaus P. The LiMAx test: a new liver function test for predicting postoperative outcome in liver surgery. HPB : the official journal of the International Hepato Pancreato Biliary Association 2010;**12**:139-46.
22 Lock JF, Kotobi AN, Malinowski M, Schulz A, Jara M, Neuhaus P, *et al.* Predicting the prognosis in acute liver failure: results from a retrospective pilot study using the LiMAx test. Annals of hepatology 2013;**12**:556-62.
23 Kaffarnik MF, Lock JF, Vetter H, Ahmadi N, Lojewski C, Malinowski M, *et al.* Early diagnosis of sepsis-related hepatic dysfunction and its prognostic impact on survival: a prospective study with the LiMAx test. Crit Care 2013;**17**:R259.
24 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. The British journal of surgery 1973;**60**:646-9.
25 Angermayr B, Cejna M, Karnel F, Gschwantler M, Koenig F, Pidlich J, *et al.* Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. Gut 2003;**52**:879-85.
26 Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, *et al.* A model to predict survival in patients with end-stage liver disease. Hepatology 2001;**33**:464-70.
27 Available from: http://optn.transplant.hrsa.gov/resources/allocationcalculators.asp?index=97.
28 Freeman RB, Jr., Gish RG, Harper A, Davis GL, Vierling J, Lieblein L, *et al.* Model for end-stage liver disease (MELD) exception guidelines: results and recommendations from the MELD Exception Study Group and Conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2006;**12**:S128-36.
29 Young AL, Rajagenashan R, Asthana S, Peters CJ, Toogood GJ, Davies MH, *et al.* The value of MELD and sodium in assessing potential liver transplant recipients in the United Kingdom. Transplant international : official journal of the European Society for Organ Transplantation 2007;**20**:331-7.
30 Asrani SK, Kim WR. Organ allocation for chronic liver disease: model for end-stage liver disease and beyond. Current opinion in gastroenterology 2010;**26**:209-13.